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Randomised trial comparing as-needed versus regular treatment with formoterol in patients with persistent asthma

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Summary
Purpose: The aim of this study was to demonstrate the equivalent efficacy of inhaled formoterol in asthmatic patients, either given as-needed or on a regular twice-daily schedule.
Methods: Randomised, open 12-week study in patients with mild to moderate asthma not adequately controlled with inhaled glucocorticosteroids alone. Patients received inhaled formoterol as needed or on a regular schedule (2×2 puffs/day with 6 μg formoterol per puff). Patients in the twice-daily formoterol group could use salbutamol as a rescue medication. The primary endpoint was the number of patients with asthma exacerbations in each group.
Results: Thirty-nine centres randomised 359 patients. The number of patients with asthma exacerbations showed neither a clinically relevant nor a statistically significant difference between groups: formoterol as-needed: 3.95% (7 of 177); twice daily: 3.45% (6 of 174). Patients in the formoterol as-needed group used significantly less formoterol (−1.5 puffs per day; $P<0.0001$). Including the saved rescue medication (up to one puff per day), total beta-2 agonist use in the formoterol as-needed group decreased by approximately 2–2.5 puffs per day.
Both formoterol treatment schedules were well tolerated. Musculoskeletal pain and tremor were less frequent in the formoterol as-needed group: headaches were slightly more frequent.
Conclusion: Formoterol given as needed and without additional beta-2 agonist, and formoterol given on a regular basis twice daily, supplemented by salbutamol as a rescue medication, appeared equally effective in this clinical study. Drug consumption was markedly lower in the former group.

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Introduction

Today, a persistent subacute inflammation is recognised as the underlying pathological basis of asthma, even in milder forms. This concept supports the use of anti-inflammatory therapies as a "long-term control medication".[1] For this reason, the early administration of inhaled glucocorticosteroids (GCS) is recommended by international and national guidelines.[2,3]

Though inhaled GCS are the mainstay of asthma therapy, these drugs alone are usually not sufficient. They do not act rapidly and may take a week or more to improve symptoms and so are inadequate to adapt therapy to intra- and between-day variations of asthma severity. Thus, "quick-relief medications"[1] inhibiting smooth muscle contraction supplement GCS therapy. Owing to their efficacy and ease of administration, rapid-acting inhaled beta-2 agonists have become the mainstay in this group of therapies. Different studies have demonstrated the superiority of GCS plus beta-2 agonist therapy. Price et al.[4] and Zetterström et al.[5] found budesonide plus formoterol more effective than budesonide alone. Formoterol plus low-dose budesonide was superior in improving lung function (forced expiratory volume in the first second; FEV_1) compared to the fourfold budesonide dose without formoterol.[6] Similar results were found for GCS plus other long-acting beta-2 agonist combinations.[7,8] Biopsy and lavage data indicate that long-acting beta-2 agonists may possess their own anti-inflammatory effect.[9] Based on such studies, the optimal treatment for mild to moderate persistent asthma as described by various guidelines is that of a GCS plus a long-acting beta-2 agonist.

Formoterol (formoterolfumaratdihydrat) is one of the most widely used selective long-acting beta-2 agonists in Europe. Formoterol induces bronchodilation within minutes[10]; its effect lasts for at least 12 h, longer than with most other beta-2 agonists. Its long duration of action is considered particularly advantageous in nocturnal asthma.[11,12]

A recently published study showed that formoterol given as needed provided better asthma control than terbutaline, also taken as needed.[13] This suggests that lower formoterol doses than the usual regular dosing schedule might also provide sufficient asthma control. Furthermore, a study in patients presenting to the emergency department with acute severe asthma showed that the long-acting bronchodilator formoterol provided equally rapid improvement of a greater magnitude and longer duration in lung function than the short-acting beta-2 agonist salbutamol, without increasing side effects.[14]

Thus, we hypothesised that (1) a regular twice-daily treatment schedule might be substituted by on-demand treatment and that (2) a short-acting bronchodilator might be withheld without impairing patient safety. Subsequently, we intended to demonstrate that formoterol given as needed compared to formoterol on a twice-daily treatment schedule plus a rescue beta-2 agonist was equally effective in asthmatic patients who continued their customary inhaled GCS therapy. The primary efficacy endpoint was the number of patients with asthma exacerbations in each group.

Methods

Patients

Thirty-nine German and Eastern European centres participated in this study and included male and female outpatients between 18 and 50 years of age who had a history of at least 6 months of mild to moderate persistent asthma. Patients were on inhaled GCS treatment in the last 4 weeks prior to enrolment, with a stable dose of up to 800 μg budesonide or equivalent. Mild to moderate asthma was diagnosed using modified global initiative for asthma (GINA) criteria[2]: Patients' FEV_1 was between 60% and 90% of the predicted value; FEV_1 reversibility within 30 min of inhaling two actuations of 100 μg salbutamol had to be $\geqslant$12%, with an increase of at least 200 mL. After the run-in period (see below) and before randomisation, FEV_1 had to be between 50% and 90% of the predicted value, accounting for a possible worsening of asthma due to changes in GCS and/or beta-2 agonist therapy during this phase. FEV_1 should not differ more than 15% from the value obtained at the screening visit. As an indicator for mild to moderate asthma, patients had to require an average of at least three puffs of salbutamol a day on at least 5 days during the run-in period, but not more than twelve puffs on any 1 day. Patients had to provide written informed consent after having received oral and written information on the study.

Patients were considered ineligible in the case of inpatient asthma treatment within 4 weeks prior to the screening visit, respiratory tract infection within 4 weeks prior to the screening visit, seasonal asthma during the study period, treatment with systemic GCS less than 3 months prior to the screening visit, or a smoking history of $\geqslant$10 pack years. During the study, treatment with oral GCS (exceptions were made for patients requiring intermittent oral GCS therapy up to 1 week as a result of respiratory infection and in the case of treatment of asthma exacerbations), sodium cromoglycate, nedocromil, systemic antihistamines, leukotriene antagonists, theophylline or anticholinergic drugs, beta-receptor blocking drugs, including eye drops was excluded.

Treatment and visits

During a 2-week run-in period, patients received budesonide according to their previous dose of inhaled GCS up to 800 μg daily and salbutamol as required, both via Novolizer® (Budecort® 200 Novolizer®, Salbu Novolizer®, Astellas Pharma GmbH, formerly Fujisawa Deutschland GmbH). Afterwards, patients were randomised to one of the following two groups: (1) formoterol 6.0 μg via Novolizer®, inhalations day by day only as needed, and (2) formoterol 6.0 μg via Novolizer®, two inhalations twice daily taken regularly in the morning and evening, i.e. a daily dosage of 24 μg formoterol.

Patients in the fomoterol as-needed group did not receive specific instructions on when to use which dose. They were free to use more than one puff at a time, but they were informed of the maximum permitted formoterol dosage, which was 12 puffs per day and a maximum of 6 puffs at a time.

Formoterol was delivered as Formotop® Novolizer® (Astellas Pharma GmbH, formerly Fujisawa Deutschland GmbH). The Novolizer® is a refillable, multidose, breath-actuated dry powder inhaler. In the formoterol Novolizer®, formoterol is bound to the excipient lactose, resulting in an optimised deposition in the airways. The respirable particle fraction is on average smaller than 5.5 μm. A cross-over study with the formoterol Novolizer® has shown efficacy and safety identical to another commercially available formoterol dry powder inhaler.[15] In patients with moderate to severe asthma, the ratio of the area under the curve for FEV_1 ($AUC_{0-12\,h}$) was 1.01 ± 0.13 for the 12 μg formulations (difference not significant).

The treatment period lasted for 12 weeks. All patients received budesonide delivered by Novolizer® at a constant dose of up to 800 μg daily (Budecort® 200 Novolizer®, Astellas Pharma GmbH, formerly Fujisawa Deutschland GmbH); this dose had to be identical to the dose during the run-in period. Patients in the formoterol twice-daily group received salbutamol via Novolizer® as a rescue medication (Salbu Novolizer®, Astellas Pharma GmbH, formerly Fujisawa Deutschland GmbH). Patients in the formoterol as-needed group were not permitted to use salbutamol and had no other rescue medication in addition to their individual formoterol dose.

On the days of the study visits, the study drugs and any other asthma medication always had to be taken after lung function tests in the presence of the investigator.

The study included five patient visits, i.e. screening (14 ± 2 days before baseline), baseline and randomisation (day 0), and visits after 4, 8 and 12 weeks of therapy (28 ± 4, 56 ± 4, and 84 ± 4 days after the baseline visit). Efficacy and safety data were determined at all visits.

Outcomes

Primary efficacy variable was the number of patients in each treatment group with an exacerbation of asthma. An exacerbation was defined as (1) need for treatment with oral GCS as judged by the investigator or (2) decrease in the morning peak expiratory flow (PEF) of more than 30% from the baseline value on two consecutive days. The baseline PEF value was determined after the run-in period and before randomisation (day 0). Furthermore, the presence of an exacerbation was derived from the presence of a corresponding documented adverse event with the MedDRA lowest level term 'Exacerbation of asthma'.

Secondary efficacy variables were: (1) time to the first exacerbation, (2) total number of exacerbations, (3) FEV_1, FEV_1% predicted, forced vital capacity (FVC), FEF_{25-75} (maximum forced expiratory flow of 25–75% of the total expiratory vital capacity), and PEF by spirometry, (4) morning/evening PEF, (5) number of inhalations of study medication (formoterol) per day, (6) number of inhalations of rescue medication (salbutamol) per day in the formoterol twice-daily group, (7) evaluation of asthma symptoms (Asthma Symptom Score; Range: 0–24)—coughing, wheezing, shortness of breath, chest tightness (0–5 rating scales), nocturnal sleep disturbance (0–4 rating scale), (8) totally asthma-controlled days, defined as (a) no nocturnal sleep disturbance *and* (b) no asthma symptoms during the day *and* (c) no rescue medication salbutamol, (9) Formoterol-use-free days in the as-needed treatment arm, and (10) Investigator's and patient's assessments of efficacy on five-step verbal rating scales.

At each study visit, the investigator measured pulmonary function by means of spirometry, and recorded FEV_1, FVC, FEF_{25-75} and PEF. Three readings were performed and the highest value regarding FEV_1 was used for evaluation. The predicted values were calculated according to the formula of the ECCS (European Community for Coal and Steel[16]). Throughout the study, pulmonary function tests were performed between approximately 8.00 and 10.00 a.m. and at approximately the same time points and in the same position (sitting or standing) for each individual patient. To avoid bias, patients had to withhold short-acting beta-2 agonists for at least four hours and long-acting beta-2 agonists for at least 12 h prior to each pulmonary function test.

For PEF at each time point, three readings were obtained; the best was recorded in the patient's diary and used for evaluation.

Safety variables were: (1) adverse events (AE), (2) blood pressure and heart rate, (3) body weight, and (4) investigator's and patient's assessments of tolerability on five-step verbal rating scales.

Sample size

Sample size was estimated for the primary endpoint, i.e. the percentage of patients with asthma exacerbations. The calculation was based on the following assumptions: (1) independent groups with a size ratio of 1:1 for the as-needed and the twice-daily treatment group, (2) one-sided *t*-test for non-inferiority at a significance level of $\alpha = 0.05$ and $\beta = 0.20$ (power = 80%), (3) expected percentage of asthma exacerbations in the as-needed and the twice-daily treatment group = 0.15 (15%), (4) Expected difference between the as-needed and the twice-daily treatment group = 0.00 (0%), and (5) irrelevant difference in the percentage of asthma exacerbations between the two treatment arms $\leqslant 0.10$ (10%).

These assumptions resulted in a sample size of $N = 158$ evaluable patients per group ($N_{Total} = 316$).

Randomisation and blinding

The random plan was drawn up by means of RANCODE Version 3.6. Randomisation was performed in separate blocks for each centre. After the run-in period, patients were randomised in consecutive order.

The investigational product was identical in both treatment arms of the study, but the dosage scheme was different. Accordingly, a blinding of the two arms was not possible and the study was performed in an open design.

Statistical methods

The primary efficacy analysis was based on the intention-to-treat (ITT) population, which included all randomised patients with at least one regular follow-up visit under study medication. For the ITT population, missing values of

efficacy endpoints were replaced by the last observation carried forward (LOCF), where appropriate. A second supportive analysis based on the according-to-protocol (ATP) population, which included all ITT population patients without major protocol violations. All protocol violations were assessed by a blinded data review committee, which decided on exclusions from the ATP analysis. The safety population, which included all patients who had taken at least one dose of the study medication formoterol, was used for safety analyses.

For the statistical analysis, centres with less than two patients per treatment group were pooled together to an artificial centre.

As described under *Outcomes*, the primary efficacy variable was the number of patients with asthma exacerbations. The analysis was based on the following set of hypotheses:

$$H_0 : p_{A-N} \geqslant p_{R-T} + 0.10 \text{ versus } H_1 : p_{A-N} < p_{R-T} + 0.10$$

with (1) p_{A-N}: = relative number of patients with asthma exacerbations in the as-needed treatment arm and (2) p_{R-T}: = relative number of patients with asthma exacerbations in the regular twice-daily treatment arm.

The above hypothesis was tested based on an exact, unconditional test for binomial differences. In addition, an exact one-sided 97.5% unconditional confidence interval for the difference of proportions was calculated. If the upper limit of this confidence interval was less than 0.10 (or correspondingly the *P*-value of the *t*-test on non-inferiority was less than 2.5%), then the null hypothesis could be rejected.

Secondary efficacy variables were analysed descriptively, with *P*-values not considered confirmatory. Statistical tests were chosen as appropriate to the scale of the variable.

The following safety variables were analysed: (1) incidence and frequency of AE, (2) course of vital signs and body weight, and (3) investigator's and patient's assessment of tolerability. All analyses were explorative.

Legal requirements and ethics

The following safety variables were analysed: (1) incidence and frequency of AE, (2) course of vital signs and body weight, and (3) investigator's and patient's assessment of tolerability. All analyses were explorative.

The study was submitted to the relevant national authorities and notified to the local authorities as required by national laws. It was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study documents were reviewed by Independent Ethics Committees or Institutional Review Boards, which gave positive opinions prior to the start of the study.

Results

Patients

Investigators screened 386 patients, of whom 27 were screening failures. Thirty-nine centres randomised the remaining 359 patients to the formoterol as-needed group ($n = 182$) or to the formoterol twice-daily group ($n = 177$). These patients comprise the safety data set.

In the two treatment groups, eight and five patients, respectively, were withdrawn, so that $n = 174$ patients in the formoterol as-needed group and $n = 172$ patients in the formoterol twice-daily group completed the study.

Of the 359 patients in the safety data set, five and three patients, respectively, in the two treatment groups were withdrawn before the first regular follow-up visit at week 4, so that the ITT data set comprised $n = 351$ patients: $n = 177$ patients in the formoterol as-needed group and $n = 174$ patients in the formoterol twice-daily group. Relevant protocol violations occurred in 13 and 6 patients of these 351 patients, so that the ATP data set comprised $n = 332$ patients: $n = 164$ patients in the formoterol as-needed group and $n = 168$ patients in the formoterol twice-daily group. The most frequent relevant protocol deviations were use of inadmissible concomitant medication and inadequate use of the rescue medication salbutamol. Disposition of patients and reasons for withdrawal are compiled in Fig. 1.

Demographics and baseline data

Relevant demographic and baseline data for both treatments are compiled in Table 1.

The two treatment groups were well balanced, which was confirmed by different tests on baseline homogeneity. Statistical tests revealed significant or near-significant centre effects for age, height, weight, gender, and FEV_1% predicted at Visit 1, which indicates that patient populations differed between centres. This diversity increases the population's representative character and thus the general applicability of the study results.

Compliance

For the treatment group receiving formoterol twice daily, compliance with formoterol intake was calculated as the total number of study days multiplied by four puffs compared to the actual number of puffs derived from the drug accountability data. Mean compliance was high with 95%. Compliance could not be calculated for the group taking formoterol as needed due to the lack of a reference value.

Analyses of efficacy—primary efficacy variable exacerbation of asthma

In the group taking formoterol regularly twice daily, six patients (3.45%) suffered an exacerbation of asthma; in the group taking formoterol as needed, these were seven patients (3.95%; ITT population; Table 2). The null hypothesis of inferiority of the as-needed therapy versus the twice-daily treatment schedule of formoterol could be rejected ($P = 0.0002$). The point estimate of difference (0.51%) as well as the upper limit of the one-sided 97.5% confidence interval ($-\infty$; 4.95%) were below 10%, the pre-specified border of a clinically irrelevant difference. Thus the as-needed treatment schedule was non-inferior to the twice-daily formoterol treatment schedule in preventing asthma exacerbations.

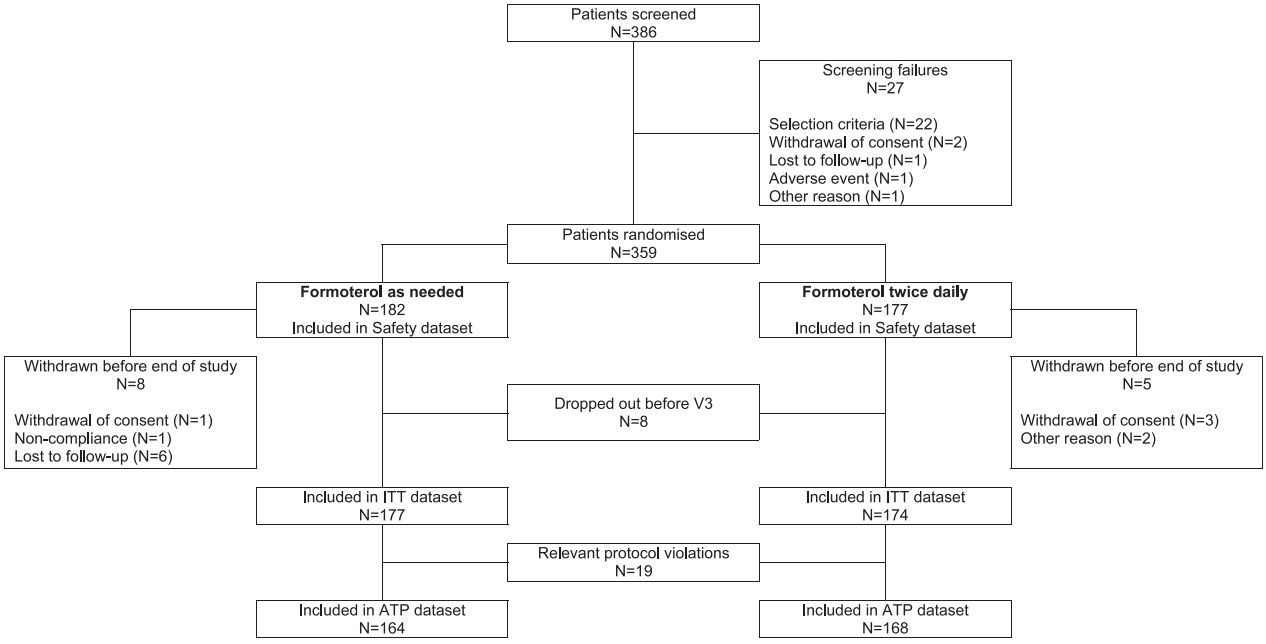

Figure 1 Disposition of patients and allocation to analysis populations. ITT: intention to treat; ATP: according to protocol.

Table 1 Baseline data (SD: standard deviation).

Demographic data	Treatment	
	Formoterol as needed	Formoterol twice daily
Total *N*—safety data set	182	177
Sex (*N* (%))		
Male	72 (39.6)	77 (43.5)
Female	110 (60.4)	100 (56.5)
Smoking history (*N* (%))		
Smoker (<10 pack years)	10 (5.5)	8 (4.5)
Non-smoker	148 (81.3)	141 (79.7)
Ex-smoker	24 (13.2)	28 (15.8)
Total *N*—ITT data set	177	174
Age (years) mean ± SD	39.5 ± 8.7	38.4 ± 8.4
Height (cm) mean ± SD	168.0 ± 8.5	169.0 ± 9.1
Weight (kg) mean ± SD	73.67 ± 14.80	74.60 ± 15.76
Body mass index (kg/m^2) mean ± SD	26.11 ± 5.02	26.02 ± 4.76
Duration of asthma disease (years) mean ± SD	9.1 ± 8.5	10.0 ± 9.1
FEV_1 (L) at day 0 mean ± SD	2.51 ± 0.54	2.57 ± 0.59
FEV_1% predicted at day 0 mean ± SD	77.23 ± 8.75	76.49 ± 8.75
FVC (L) at day 0 mean ± SD	3.24 ± 0.80	3.31 ± 0.79
PEF (L/s) at day 0 mean ± SD	5.16 ± 1.98	5.17 ± 1.81
Reversibility test		
Increase of FEV_1 over initial value (%) mean ± SD	23.5 ± 10.3	23.3 ± 9.4

Data for the ATP population were similar, with a point estimate of difference of −0.52% and an upper limit of the one-sided 97.5% confidence interval of 3.83% (Table 2). The analyses for both definitions of asthma exacerbation (according to the number of AE with the applicable MedDRA term and according to a clinical definition based on a repeated decrease of PEF or a progressive increase of asthma symptoms) gave corresponding results.

Time to first exacerbation

The mean time to first exacerbation was approximately 1 week longer in the formoterol as-needed group (53.0 ± 24.3 days) compared to the formoterol regularly twice-daily group (46.3 ± 12.6 days). This difference was not statistically significant. No patients suffered from second exacerbations.

Table 2 Exacerbation of asthma based on reported adverse events.

Population	Percentage (number) of patients with asthma exacerbations		Difference (as needed—twice daily)	One-sided 97.5% confidence interval*	*P*-value*
	Formoterol twice daily	Formoterol as needed			
ITT	3.45% (6 of 174)	3.95% (7 of 177)	0.51%	$(-\infty; 4.95\%)$	0.0002
ATP	3.57% (6 of 168)	3.05% (5 of 164)	−0.52%	$(-\infty; 3.83\%)$	<0.0001

*Unconditional exact test for non-inferiority for a binomial difference.

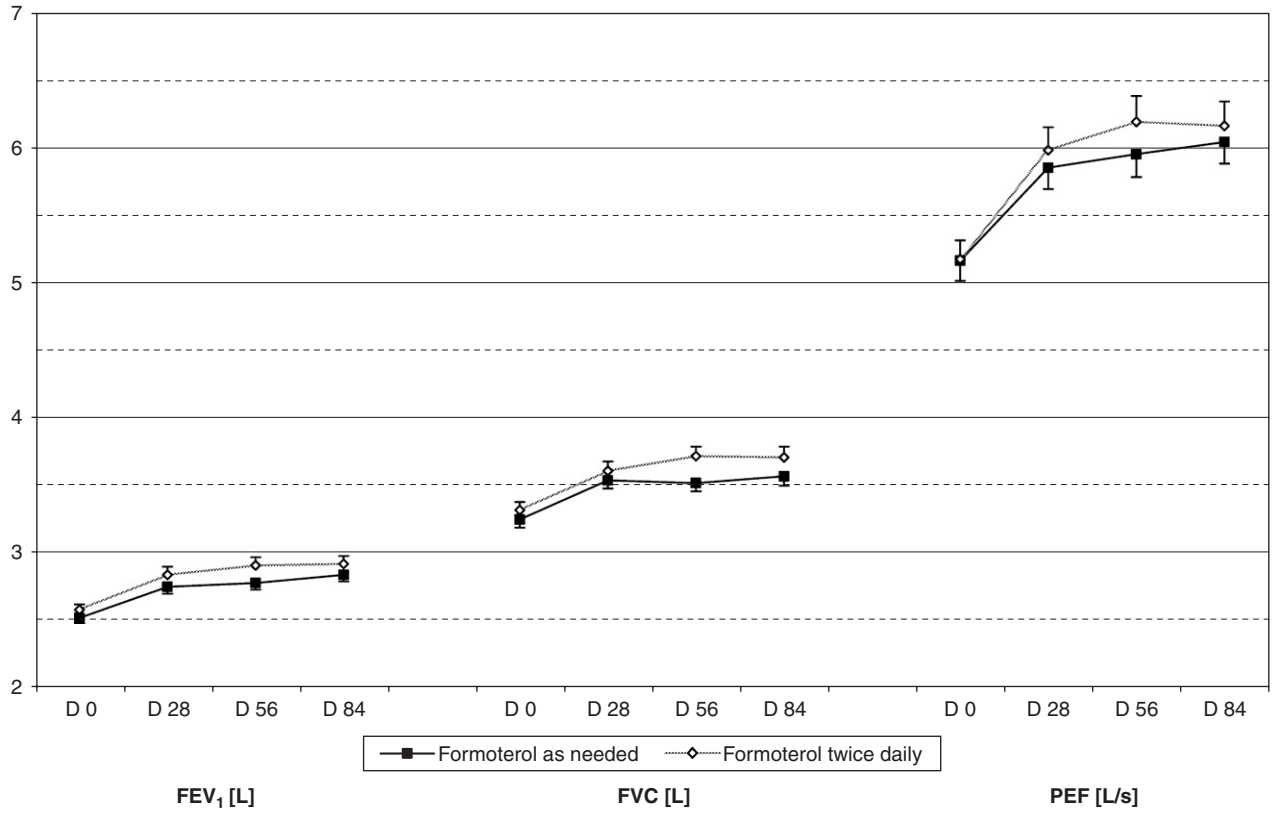

Figure 2 FEV_1, FVC, and PEF by spirometry—mean + or − SEM (standard error of the mean); highest value; ITT data set.

Spirometry data

Relevant spirometry data are given in Fig. 2. Parameters increased to a similar extent in both treatment groups until the last examination (day 84). The extent of improvement generally corresponded to 10–20% of the mean starting values. Improvement was somewhat quicker or larger in the formoterol twice-daily group for FEV_1, FVC, and PEF, and in the formoterol as-needed group for FEF_{25-75}. With the exception of FVC data on day 56, the differences between groups were not significant. ITT and ATP analyses gave compatible results.

In the formoterol as-needed group, mean morning PEF recordings as self-determined by a pocket peak flow metre increased gradually from 366 ± 108 L/min in the 2-week run-in period to 385 ± 108 mL/min in Week 9–12, i.e. by 19 mL/min. In the formoterol twice-daily group, the increase was 29 mL/min and thus larger. The difference between groups approached statistical significance for the weeks 5–8 and 9–12 data ($P = 0.0624$ and 0.0562, respectively). Data for the ATP population were numerically similar, but did not approach statistical significance. Evening PEF was numerically mostly higher than morning PEF, and the same trends as described for morning PEF were observed.

Use of formoterol and salbutamol

Patients in the formoterol as-needed group used between 41 and 45 puffs less per 4-week period than patients in the formoterol twice-daily group (see Table 3), corresponding to an average of approximately 1.5 saved puffs of formoterol per day. The difference between groups was highly significant for all three periods ($P<0.0001$). Between 7%

Table 3 Number of formoterol inhalations (SD: standard deviation).

Total number of inhalations of study medication (formoterol) per visit	Visit		
	Weeks 1–4	Weeks 5–8	Weeks 9–12
Formoterol as needed			
Mean ± SD	70.9 ± 45.7	67.5 ± 47.0	66.7 ± 49.2
N	175	174	172
Formoterol twice daily			
Mean ± SD	111.9 ± 8.2	110.5 ± 11.7	111.3 ± 10.6
N	173	173	171

and 7.5% of patients in the formoterol as-needed group required more than four puffs per day, the regular dose in the formoterol twice-daily group.

Patients in the formoterol twice-daily group needed an average of 29 ± 41 puffs of salbutamol in the first four study weeks and 17 ± 34 puffs in the last four study weeks. This is an average of 0.60–1.03 puffs per day. Patients in the formoterol as-needed group were not allowed to take any puffs of salbutamol.

Adding up the salbutamol dose and the higher use of formoterol in the formoterol twice-daily group, patients under this schedule had a higher consumption of beta-2 agonists by an average of 2–2.5 puffs per day.

Asthma symptom score

The mean subscores for wheezing, shortness of breath, chest tightness, coughing, and sleep disturbance as well as the mean Total Asthma Symptom Score decreased gradually and to a comparable extent in both treatment groups (Total Asthma Symptom Score at study end: formoterol as-needed: −1.40 ± 2.43 versus baseline; formoterol twice daily: −1.56 ± 2.16 versus baseline).

Asthma-controlled days and formoterol-use-free days

The mean sum of asthma-controlled days increased steadily from 0.6 or 0.4 days in the run-in period to an average of 6.6 ± 9.1 days in the formoterol as-needed group and 10.5 ± 11.2 days in the formoterol twice-daily group during the last four study weeks. The difference between groups was statistically significant for the two periods weeks 5–8 and 9–12 ($P \leqslant 0.0005$).

The mean number of formoterol-use-free days (only valid for the as-needed treatment arm) increased from 3.8 ± 6.8 during weeks 1–4 to 4.7 ± 8.0 during weeks 5–8 and finally to 5.5 ± 8.7 during weeks 9–12.

Analysis of efficacy—investigator's and patient's assessment of efficacy

Investigators assessed approximately 90% of the patients as markedly or moderately improved, the two highest ranks on the five-step verbal rating scale used. The difference between the two groups was not significant. Patients assessed the efficacy of formoterol twice daily more favourably than the efficacy of formoterol as needed (94.2% versus. 85.7% better or much better; 65.1% versus 53.7% much better). This difference between groups was statistically significant ($P = 0.0064$).

Analysis of safety

Both formoterol treatment schedules were well tolerated in this study. Numerically, AE were less frequent (73 versus 84 AE) and less severe (0 versus 3 severe AE; 23 versus 28 moderately severe AE) in the formoterol as-needed group, and in this group treatment-related AE were also less frequent (2 versus 6).

The distribution of AE to the different MedDRA System Organ Classes was generally similar. Musculoskeletal pain and tremor were less frequent in the formoterol as-needed group; headaches were slightly more frequent.

Two serious AE occurred during the treatment phase of the study, both in the formoterol twice-daily group (death caused by miliary tuberculosis; hospitalisation for serous otitis; both approximately two months after start of therapy). Both were unrelated to the formoterol medication and thus do not indicate an increased risk of the twice-daily application schedule.

Vital parameters such as body weight, blood pressure and pulse rate showed neither material change during the study nor any influence of the treatment schedule.

The overall safety assessment showed no major difference between treatment schedules. Tolerability was assessed as very good or good by over 96% of investigators and patients in both groups.

Discussion

In this study, we demonstrate equivalent efficacy with regard to the primary endpoint asthma exacerbations of a treatment regimen with formoterol used as needed and a treatment with formoterol on a twice-daily basis in mild to moderate persistent asthma. At 3.45–3.95% over 3 months, the rate of asthma exacerbations we observed was lower than the 15% anticipated for sample size calculation. Using comparable definitions of exacerbation, rates corresponding to approximately 15% over 3 months had previously been observed by Tattersfield[13] and by Pauwels[17], both in studies

with formoterol and inhaled GCS. However, in these studies inhaled GCS were not standardised, but used according to real-life conditions, and no separate rescue beta-2 agonist was supplied. Our absolute rates are more in line with findings from the FACET trial,[6] where patients received formoterol twice daily (24 μg total daily dose) in addition to budesonide 100 or 400 μg twice daily (200 or 800 μg total daily dose). Here, the rate of severe exacerbations—identical to our definition of an exacerbation—was 19% and 30%, respectively, over a 12-month period, depending on the budesonide dose. In our study, the budesonide dose was approximately 520 μg/day and thus in between the low and the high dose of the FACET trial. Accordingly, our results still show a somewhat better control of asthma exacerbations than the 6.4% expected from the FACET trial, linearly correcting for GCS dose and study duration.

Our efficacy results for twice-daily formoterol supplemented by a rescue medication compare well with the historical benchmarks. Thus, it is encouraging to find that formoterol given only as needed and without rescue medication controlled asthma exacerbations, the primary efficacy endpoint, to an equivalent extent. The lower than expected rate of asthma exacerbations reduced the statistical power to verify a correspondingly smaller range of an irrelevant difference for the primary endpoint. However, both the point estimate and the upper limit of the 97.5% confidence interval for differences between groups—below 1% and below 5%, respectively—confirm the clinical equivalence of both dosing schedules.

Asthma symptoms improved to a comparable extent in both groups, but numerical mostly non-significant differences between groups in secondary endpoints generally favoured the twice-daily formoterol schedule. The number of asthma-controlled days was significantly different between groups, with a difference of up to four days per four-week period in favour of the formoterol twice-daily group. Patients' subjective efficacy ratings were also significantly higher for twice-daily formoterol.

Overall, these data indicate that in asthma patients using regular inhaled GCS (1) formoterol on an individual dosing schedule is sufficient to avoid severe asthma exacerbations and (2) patients can be trusted to find this dose. Though we do not have data on this aspect, differences in secondary and less severe efficacy endpoints could be explained by three reasons. First, the availability of two inhalation devices, containing formoterol and a rescue medication, might make patients feel more secure than only one device (with formoterol). From a psychological point of view, this could result in a more favourable rating of subjective endpoints in the formoterol twice-daily group. Second, patients may forget dosing altogether if they are allowed to deviate from a structured twice-daily application schedule. Third, patients could prefer to tolerate a certain amount of less severe asthma symptoms for the benefit of reduced drug consumption.

Indeed, drug consumption was markedly lower in the formoterol as-needed group. Adding formoterol and salbutamol puffs, dosing formoterol as needed reduced the total use of a beta-2 agonist by approximately 2–2.5 puffs per day: a reduction of 1.5 puffs of formoterol per day plus the saved salbutamol of approximately 0.6–1.0 puffs per day. Thus, the amount of drug saved corresponded to nearly half of the conventional dose of approximately five puffs with regular twice-daily dosing: two times two puffs of formoterol per day plus up to one puff of a rescue beta-2 agonist. Reducing the need for beta-2 agonists by almost 50% without increasing the risk of an asthma exacerbation appears clearly clinically relevant.

Furthermore, it is interesting to look at the consumption of beta-2 agonists from the perspective of individual patients. Whereas the recommended formoterol dosing schedule is twice daily, whether needed or not, data from the formoterol as-needed group show that actually more than 35% of the patients did not require this drug on a daily schedule at all (see Table 4). An increasing proportion of patients even did not need formoterol for *more* than seven days in subsequent four-week periods. During the first four study weeks, every fifth patient (19.9%) fell into this category, and during the last four study weeks this applied to almost every third patient (29.5%). In the last study period, every sixth patient (17.3%)—who would usually have received daily formoterol—required a beta-2 agonist on less than 50% of the days during this month.

Use of formoterol showed significant treatment-by-centre interactions at all time points and in both analysis populations. Thus, contrary to the *lower mean use* of formoterol in the formoterol as-needed group, in some centres the patients in this group obviously used *more* formoterol than the patients in the formoterol twice-daily group. The exact reason for this finding is unknown. It may reflect patient populations unresponsive to instructions, who have decided to stick to the usual twice-daily inhalation schedule. Without a second beta-2 agonist as a rescue medication, any rescue puffs taken would increase the total formoterol dose over four puffs per day. Though contrary to our intentions, such patient behaviour is not critical. Taking into account the equivalence of both treatment schedules in the control of asthma exacerbations, it appears safe to offer patients the as-needed formoterol approach when applying our results to everyday practice.

When planning the study, we were unsure whether the open design introduced any bias through patient preference, and if so, in what direction. Results now give an answer to this question. Despite a comparable efficacy of both treatment schedules in the investigators' assessment of general efficacy, the patients assessed the regular twice-daily treatment schedule more favourably. As already indicated above, this difference might at least partly be based on a psychological rationale: patients in the formoterol as-needed group may have felt less secure with only

Table 4 Number of formoterol-use-free days; weeks 9–12; formoterol as-needed group; ITT population.

Number of formoterol-use-free days in weeks 9–12	Formoterol as needed	
	N	%
0	106	61.27
1–7	16	9.25
8–14	21	12.14
>14	30	17.34

one inhalation device, i.e. without rescue medication. We suggest that this subjective shortcoming may be overcome by intensified patient counselling, including the information that formoterol is classified by international asthma initiatives as a rapidly acting drug,[2,18] and a second beta-2 agonist is not required to prevent asthma attacks more efficiently.

Both treatment schedules were well tolerated. Headaches, tremor and muscle pains are known side effects of beta-2 agonists. It seems plausible that a reduction of the dose, such as was seen in the formoterol as-needed group reduces tremor and muscle pains. There is no obvious reason for the minor increase of headache frequency in the formoterol as-needed group; withdrawal effects stimulated by an extension of the dosing interval are previously unreported.

It is a clinical reality that many patients prescribed a fixed dosing schedule use a beta-2 agonist only as needed. Our study showed that this is acceptable. We found no difference in the incidence of severe asthma attacks. A fixed dosing schedule and the availability of a second—short-acting—beta-2 agonist may control less severe symptoms better, but the difference is of marginal clinical relevance and appears well balanced by the amount of beta-2 agonist saved with the as-needed approach. Furthermore, this study is a point in favour of individual versus fixed combination drugs including a beta-2 agonist. Fixed combination drugs do not allow an individual step-up or step-down of either component and thus forego the possibilities for major reductions of drug exposure, which may, like in our study, range up to 50%.

When prescribing long-acting beta-2 agonists in an as-needed schedule, patients should be instructed that this approach does not apply to their inhaled GCS. In the light of recent findings on their safety, regular therapy with GCS should always accompany the long-term use of long-acting beta-2 agonists.[18,19]

As a conclusion and based on a comparable efficacy in preventing asthma exacerbations and a markedly lower drug consumption compared to a regular twice-daily formoterol application schedule, dosing formoterol (Formotop® Novolizer®, Astellas Pharma GmbH, formerly Fujisawa Deutschland GmbH) only as needed possesses a positive benefit-risk profile. Due to its multicentre design and the inclusion of a diverse patient population, the results of this study are representative and applicable to a general population with mild to moderate asthma.

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